REMARKS

Status of the Claims

Claims 14, 16, 18 to 27, 30 to 41, and 45 to 53 are currently pending. Claim 16 has been amended. Claims 1 to 13, 15, 17, 28, 29, and 42 to 44 have been cancelled without prejudice or disclaimer of the subject matter claimed therein. Claims 22 to 27, 30 to 41, and 45 to 53 have been withdrawn as being directed to a nonelected species. Accordingly, claims 14, 16, and 18 to 21 are currently under examination.

Amendment to the Claims

Claim 16 has been amended to remove the term "treatment" simply to maintain proper antecedent basis with claim 14 from which claim 16 depends. Applicant submits that this amendment does not result in a reduction of the scope of claim 16 since "therapy" would necessarily encompass a treatment component.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner asserts that the term "treatment" as recited in claim 16 lacks antecedent basis in view of the dependency of claim 16 on claim 14.

Applicant has deleted the term "treatment" from claim 16 with the understanding that such a deletion in no way narrows the scope of claim 16, since "therapy" would encompass a treatment component. In view of this amendment, Applicant respectfully requests that this rejection be withdrawn.

Rejection under 35 U.S.C. § 102(b)

The Examiner has maintained his rejection of claims 14, 16, and 18-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Gustafsson as evidenced by "*The Complete Drug Reference*" and Kralova.

More specifically, the Examiner asserts that Gustafsson anticipates the claimed invention because of the alleged explicit disclosure in Gustafson (on page 6, lines 1-10) that low molecular weight thrombin inhibitors, such as a prodrug of melagatran, are acceptable for use in cholesterol-lowering therapy. Further, the Examiner relies on (1) "*The Complete Drug Reference*" for allegedly indicating a correlation "between a therapy for lowering cholesterol in a

patient which is associated with lowering the risk of ischemic heart disease..." and (2) Kralova for allegedly teaching a relation between the progressive phase of ischemic heart disease and high cholesterol. Finally, the Examiner appears to assert that the alleged similarity between the clinical trial protocol (Example 1) described in the subject application in terms of dosage, compound and patient population to the trial described in Gustafsson, demonstrates the effectiveness of the melagatran prodrug for the treatment of ischemic disorders.

Applicant respectfully submits that the claims as they stand are directed to a method of lowering cholesterol comprising administering melagatran or a pharmaceutically acceptable derivative thereof to a patient in need of such therapy.

In contrast, Gustafsson relates to the use of melagatran and its derivatives in the treatment of ischemic disorder in a patient having or at risk of atrial fibrillation (AF), such as non-valvular atrial fibrillation (NVAF). On page 1, paragraphs 2 and 3, Gustafsson describes AF as "grossly disorganized atrial electrical activity that is irregular in respect of both rate and rhythm" and characterizes patients with AF as having "no visually discernible timing pattern in atrial electrical activity when measured by surface ECG, or in electrogram sequences recorded by catheter electrodes." Moreover, such patients may experience "irregular heartbeat, palpitations, discomfort, dizziness and/or angina pectoris." Gustafsson also states that "current drug therapies for AF include antiarrhythmic drugs, administered with a view to re-establishing a normal heartbeat, and anticoagulant and/or thombolytic drugs, administered with a view to preventing thromboembolism and/or cerebral stroke" (page 2, lines 11-14). Gustafsson does not teach or suggest the use of melagatran to lower cholesterol in a patient. Moreover, the patient population of Gustafsson is defined as those having or at risk of AF.

The section of Gustafsson cited by the Examiner as an "explicit disclosure that low molecular weight thrombin inhibitors, such as a prodrug of melagatran are acceptable for use in cholesterol-lowering therapy..." is shown below:

> "...patients with, or at risk of, NVAF. The skilled person will appreciate that patients with NVAF who are at risk of stroke include elderly patients generally (e.g. those with an age of greater than 75 years); patients with complicating health factors, such as hypertension,

> left ventricular dysfunction (e.g. left ventricular ejection fraction (LVEF) of less than 40%), symptomatic congestive heart failure, diabetes mellitus (especially in those patients of 65 years of age or greater) and/or coronary heart or artery disease (especially in those patients of 65 years of age or greater); and/or patients with a history of stroke, TIA and/or systemic embolism, all of which factors may predispose such patients to stroke and/or thromboembolic events."

Applicant submits that there is nothing in this description by Gustafsson that supports the above assertion by the Examiner. Rather, this section clearly and simply indicates a profile of a population group who suffers from non-valvular atrial fibrillation (NVAF) and who are also likely at risk of stroke. A person of ordinary skill in the art would find no discernible link based on this section (or any other section) of Gustafsson between a patient requiring cholesterol-lowering therapy and a patient requiring treatment of NVAF. That a general link may exist between cholesterol and ischemic heart disease is of no relevance in assessing the patentability of the claims in the subject application that are directed to a methodology that is different from the methodology taught in Gustafsson. Stated differently, Gustafsson relates to the treatment of a patient with, or at risk of, NVAF, which represents a specific subset of cardiovascular diseases. Cholesterol-based diseases also represent a subset of cardiovascular diseases, but a completely different subset.

The specification of the subject application describes the patient population as those that would benefit from the claimed treatment of lowering cholesterol. As an example, the specification on page 6, lines 7 to 23 states that a "cholesterol-lowering therapy includes any therapy that results in beneficial modifications of serum profiles of total cholesterol, lipids (including triglycerides), lipoproteins, or apolipoproteins . . . ." Accordingly, the claimed method is directed to treating patients that would benefit from reduced cholesterol levels, which is quite different from the method disclosed by Gustafsson, directed to treating patients having or at risk of AF.

A patient requiring cholesterol-lowering therapy is different from a patient requiring treatment of ischemic disorder because these two groups of patients are associated with different

symptoms and therefore are treated differently. A patient having AF may not have high cholesterol levels, while a patient having high cholesterol level may not have AF. Thus, there is no discernible link between these two groups of patients and a person of ordinary skill in the art would not expect to treat these two distinct types of disorders using the same methodology.

The differences between patients having AF and patients having high cholesterol levels can be found in a standard drug reference textbook, such as *The Complete Drug Reference,* 34th Edition, Martindale, pages 809 to 841 (pages 810 to 814 and 823 to 825 were submitted with the previously filed response). As an example, column 1, page 813 of *The Complete Drug Reference,* describes "Angina pectoris," which is associated with AF, "as a syndrome that arises from an inadequate myocardial oxygen supply (myocardial ischemia) and is part of the spectrum of coronary or ischemic heart disease," and explains that ischemia occurs when blood flow either cannot be increased or is reduced. As discussed on page 813, column 2, treatment of angina pectoris includes the use of anticoagulants. Page 810 of *The Complete Drug Reference* provides examples of anticoagulants such as low molecular weight heparins, which are direct anticoagulants, and warfarin, which are indirect anticoagulants. Accordingly, current drug therapies for treating ischemic disorders in patients having AF include anticoagulants, which is also taught by Gustafsson.

In marked contrast, cholesterol-based diseases are readily distinguisable from AF. As shown on column 2 on pages 823 to column 1 on page 825 of *The Complete Drug Reference*, hyperlipidemias, which is associated with high cholesterol levels, are treated with lipid regulating drugs such as statins, bile-acid binding resins, nicotinates and omega-3 triglycerides (columns 2 and 3 on page 811).

Clearly, the lipid regulating drugs used to lower cholesterols and the anticoagulants used to treat AF are structurally and functionally distinct drugs. Thus, AF and cholesterol-based diseases are completely separate disorders requiring different drugs to treat different patients. Moreover, the cited reference, Gustafsson relates to the use of melagatran and derivatives thereof as a direct thrombin inhibitor to improve anticoagulant treatment for patients with an ischemic disorder. Gustafsson does not teach or suggest the use of melagatran to lower cholesterol in a patient in need thereof. Moreover, neither Gustafsson nor *The Complete Drug Reference* teaches that anticoagulants are effective in lowering cholesterol in a patient.

The Examiner has asserted that because Example 1 in the subject application describes a clinical trial that is allegedly similar to the protocol described in Gustafsson in terms of dosage, compound and patient population, the inventions must be the same. Applicant points out that the Gustafsson protocol does not contemplate or assess the beneficial effects of ximelagatran on cholesterol, low-density lipoproteins, triglycerides and/or apolipoprotein. It is in view of this new and unexpected beneficial property that a novel treatment of a completely new set of diseases has been discovered and claimed by Applicant.

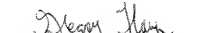
At least for the above-discussed reasons, Applicant submits that the claims of the subject application are patentably distinct from Gustafsson as evidenced by "*The Complete Drug Reference*" and Kralova.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicant respectfully requests entry of the amendments, reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should an interview be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
Morgan, Lewis & Bockius LLP



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